SEQ ID NO:44 and SEQ ID NO:46, and said portion of *Clostridium botulinum* type E toxin is selected from the group consisting of SEQ ID NO:54 and SEQ ID NO:56.

28. (Once amended) The soluble and neutralizing vaccine of Claim 11, wherein said portion of *Clostridium botulinum* type A toxin is selected from the group consisting of SEQ ID NO:26 and SEQ ID NO:36.

REMARKS

Status of the Application

Claims 10-14 and 25-28 are pending in the application.

Claims 10-14 and 25-28 have been amended to more specifically describe Applicant's invention by reciting that the vaccine is "soluble,"[1] and "neutralizing."[2]

Applicant's amendments do not introduce new matter.

The Examiner advanced the following grounds of rejection:

1. Claims 10-14 and 25-28 were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement;

2. Claims 10-14 and 25-28 were rejected under 35 U.S.C. § 112, second paragraph for being allegedly indefinite;

3. Claims 10-14 and 25-28 were rejected under 35 U.S.C. § 103(a) for alleged obviousness over Thompson *et al.* in view of Binz *et al.*, Roitt , LeClerc *et al.*, Kleid, and Siegel; and

4. Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) for being allegedly obvious in view of Thompson *et al.*, Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel and further in view of Ford *et al.* The Examiner's rejections are addressed below.

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[1] Support for this amendment is found in the specification at Example 39, pages 235-238, which discloses purification of soluble fusion proteins containing type B toxin from fermentation cultures, and Example 44, pages 250-251 which discloses the induction of totally soluble fusion proteins containing type E toxin.

[2] Support for this amendment is found in the specification at Example 26, pages 202-203, wherein it is disclosed that the pHisBot protein is an effective immunogen, Example 27, pages 204-205 which discloses that immunization with the recombinant pHisBot protein generates neutralizing antibodies, Example 36, pages 229-230 disclosing the generation of neutralizing antibodies using the recombinant pHisBotB protein, Example 42, pages 247-248, disclosing the generation of neutralizing antibodies using the recombinant pHisBotE protein.

1. Rejection of Claims 10-14 and 25-28 Under 35 U.S.C. § 112, First Paragraph

Claims 10-14 and 25-28 were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement.[3] Applicant cannot agree for two reasons. First, the Examiner persists in failing to establish a *prima facie* case of lack of enablement. In addition, assuming a *prima facie* case of non-enablement is made (which it is not), the enclosed declaration by Dr. James A. Williams rebuts any alleged non-enablement.

A. A *prima facie* case of non-enablement is not established

The Examiner is respectfully reminded that the burden of establishing a *prima facie* case of non-enablement rests squarely with the Examiner. This burden requires the Examiner:

> ". . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure *and* to back up assertions of its own with *acceptable evidence or reasoning* which is inconsistent with the contested statement."[4]

The Examiner continues to adhere to the approach of presenting conclusory statements which lack explanation, evidence and reasoning. This will be demonstrated by the following perusal of **each** of the Examiner's statements.

The Examiner first summarizes some of Applicant's arguments presented in Applicant's Amendment mailed to the Office on November 24, 1997 in the parent application (hereinafter, the "November Amendment") as follows:

> "Applicant argues that a *prima facie* case of non-enablement has not been established. Applicant argues that the biological activity of a protein as a vaccine does not required knowledge of its structure. Applicant further argues that art-accepted neutralization assays can be used to successfully determine the biological activity of portions of Clostridium botulinum type A, B, and E toxin."[5]

Since these statements summarize Applicant's (rather than the Examiner's) arguments, they clearly are not part of the Examiner's *prima facie* case of non-enablement.

Next, in an attempt to rebut Applicant's above-summarized argument, the Examiner makes the following comment: "However, Applicant's claims read on portions as small as one

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[3] Office Action, page 2, item 3.

[4] (Emphasis added) *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

[5] Office Action, page 2, item 5.

amino acid."[6] This comment is factually incorrect. The specification provides a clear definition for the term "portion," explaining that it encompasses a minimum of four (not one) amino acids. It states:

> "As used herein the term "portion" when in reference to a protein (as in "a portion of a given protein") refers to fragments of that protein. The fragments may range in size from four amino acid residues to the entire amino acid sequence minus one amino acid."[7]

Indeed, the Examiner's misunderstanding of the term "portion" is contradicted by the Examiner's two subsequent statements which recognize that the portions encompass **four** or more amino acids, **not one** amino acid. For example, the Examiner states that "The specification indicates that 'fragments may range in size from *four* amino acid residues to the entire amino acid sequence minus one amino acid.'"[8] Because the Examiner's comment is factually incorrect, it cannot provide acceptable reasoning of non-enablement.

The Examiner then purportedly argues that: "There is *insufficient* teaching and guidance in the specification to indicate to one of skill in the art which 'portions', wherein portions as small as four amino acid residues are considered, if administered, would result in the production of the neutralizing antibodies and thus the protection recited in the claims."[9] This statement is conclusory; it concludes only that the specification's teaching and guidance is "insufficient" without explaining **why** the mouse neutralization assay which is (a) art accepted for evaluating anti-botulinal antibodies,[10] (b) disclosed in detail in the specification,[11] and (c) successfully used to determine the biological activity of **portions** of both the

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6 Office Action, page 2, item 5.

7 Specification, page 19, lines 3-6.

8 (Emphasis added) Office Action, page 2, item 5.

9 (Emphasis added) Office Action, sentence bridging pages 2 and 3.

10 Specification pages 181, lines 15-19.

11 Specification, paragraph bridging pages 178-179; page 181, lines 15-19, and lines 27-28; page 182, lines 1-21; page 181, lines 10-28; pages 182-183; page 184, lines 1-17; paragraph bridging pages 211-212; page 212, lines 3-5, and lines 9-23.

Clostridium botulinum type B toxin[12] and type E toxin[13] that are recited in rejected amended Claim 10 is "insufficient."

The Examiner continues to state that "The specification fails to provide *sufficient* guidance to enable one of ordinarily skill in the art to make and use the claimed protein in a manner reasonably correlated with the broad scope of the claims including any number of fragments or portions of any size."[14] This is yet another conclusory statement which conspicuously lacks support; no explanation is offered as to **why** the specification's above-discussed disclosure would be "insufficient" to determine the biological activity of portions of types B and E toxins when such disclosure provides a detailed description of an art-accepted assay which succeeded in establishing the activity of exemplary portions of types B and E toxins.

Next, the Examiner attempts to imbue credibility to her next argument by providing case law. She states "*In re Fisher*, 1666 USPQ 1924 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Here, the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue."[15] Without commenting on the holding of *In re Fisher*, the Examiner's statement simply concludes that experimentation is "unnecessarily, and improperly extensive and undue." Yet again, there is no explanation as to **why** this is so.

The Examiner then states that "In addition, the specification does not enable the myriad of fusion proteins encompassed by the claims in view of the use of 'comprising' language and with the reciting of 'one or more' in the amended claims. One of skill in the art could not practicably generate neutralizing antibodies offering the protection recited in the claims without undue experimentation."[16] These statements suffer from two shortcomings. First, the statements appear to hinge on the Examiner's perception that a claim which comprehends a "myriad" of compositions is *ipso facto* non-enabled. Such perception is

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12 Specification, Example, 36, pages 229-230.

13 Specification, Example 42, pages 247-248.

14 (Emphasis added) Office Action, page 3, first paragraph.

15 Office Action, page 3, first paragraph.

16 Office Action, page 3, first paragraph.

legally unsound. Enablement is not determined by the number of embodiments comprehended by the claims, but whether it is within the ordinary skill in the art to make and use these embodiments. Second, these statements do not establish a *prima facie* case of non-enablement as they fail to explain **why** it is not possible, given the teachings of the present specification, to evaluate the recited fusion proteins using the art-accepted assay which is disclosed in the specification and which was successfully used with portions of *Clostridium botulinum* types B and E toxins.

The Examiner then ends by stating that "In view of the lack of predictability of the art to which the invention pertains and the limited working examples, the state of the prior art, the lack of guidance in the specification and the breadth of the claims, it would take undue experimentation to practice the invention as broadly claimed."[17] This statement is notable, not for what it says, but for what it omits to say. Specifically, there is no explanation of **why** there is a "lack of predictability" in producing the recited vaccines, **why** the working examples which disclose the biological activity of toxin A, two portions of toxin B (SEQ ID NOs: 44 and 46) and of two portions of toxin E (SEQ ID NOs:54 and 56) is "limited," **what** the state of the art is and **why** it supports non-enablement, **why** the specification's guidance is lacking in view of the breadth of the claims, and **why** experimentation is undue.

In sum, each of the Examiner's statements can be characterized only as a conclusion which lacks an explanation of **why** such conclusions were reached. Moreover, the Examiner does not advance acceptable **evidence** or **reasoning** which contradicts the specification's teaching of the suitability of the mouse neutralization assay to determine the biological activity of any portion of the *Clostridium botulinum* toxins of amended Claim 10 and claims dependent therefrom. For these reasons, a *prima facie* case of non-enablement is not established. Since Applicant need not respond on the merits to a rejection that is improper for failure of the PTO to make a *prima facie* case for non-enablement,[18] withdrawal of the reaction is respectfully requested.

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[17] Office Action, page 3, first paragraph.

[18] *In re Armbruster*, 512 F.2d 676, 185 USPQ 152 (CCPA 1975).

B. Evidence in rebuttal of a *prima facie* case of non-enablement

Applicant may rebut an Examiner's doubts about enablement by any one of three approaches, namely, pointing to details in the disclosure, providing factual affidavits under 37 CFR 1.132, or citing references to show what one skilled in the art knew at the time of filing the application.[19] Assuming, without conceding, that a *prima facie* case of non-enablement was made, Applicant rebuts both by pointing to details in the disclosure, and with a factual affidavit by Dr. James A. Williams.

i. The specification provides general and specific guidance on making and using the vaccines of Claim 10

As discussed in the November Amendment, the specification provides extensive guidance on how to test the neutralizing activity of **any portion** of a *Clostridium botulinum* type B and/or type E toxin. Briefly, the specification teaches that a vaccine's activity in provoking neutralizing antibodies in a host animal may be characterized using an **art-accepted** mouse neutralization assay.[20] In addition, step-by-step **details** on how to use this assay are extensively provided using *Clostridium botulinum* type A toxin.[21] Furthermore, the specification demonstrates the **successful use** of the assay to determine the neutralizing activity of the C fragment of type B[22] and E toxins,[23] which are encompassed by independent amended Claim 10. The use of this assay to determine the biological activity of any portion of type B and type E toxins would follow steps similar to those disclosed in the specification. It is thus submitted that the specification's disclosure is sufficiently enabling for a vaccine containing any portion of a Clostridium botulinum type B and/or type E toxin.

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[19] MPEP 2164.05.

[20] Specification, page 181, lines 15-19.

[21] Specification, paragraph bridging pages 178-179; page 181, lines 15-19, and lines 27-28; page 182, lines 1-21; paragraph bridging pages 182 and 183; page 183, lines 4-23; page 184, lines 1-17; paragraph bridging pages 211-212; page 212, lines 3-5, and lines 9-23.

[22] Specification, Example 36, pages 229-230.

[23] Specification, Example 42, pages 247-248.

ii. Affidavit Under 37 CFR 1.132 by Dr. James A. Williams

The Examiner's assertion that "[o]ne of skill in the art could not practicably generate neutralizing antibodies offering the protection recited in the claims without undue experimentation"[24] is rebutted by Dr. Williams' attached declaration. Dr. Williams' declaration confirms that "[a]ny portion of *Clostridium botulinum* type B and type E toxins which is at least four (4) amino acids long and which is fused to a non-toxin protein (*e.g.*, a polyhistidine sequence) may be made by one of ordinary skill in the art using the teachings of the present specification in combination with routine molecular biological techniques and a variety of commercially available prokaryotic and eukaryotic vectors."[25] As to determining the neutralizing activity of any such portion, Dr. Williams declaration establishes that the biological activity of "**any portion**" of either *Clostridium botulinum* type B or type E toxin in generating neutralizing antibodies may readily be determined using the art accepted mouse neutralization assay which was available and routinely used **six years** prior to the filing date (*i.e.*, August 28, 1996) of the instant application.[26]

In view of the above arguments and declaration, the rejection of Claims 10-14 and 25-28 under 35 U.S.C. §112, first paragraph should be withdrawn.

2. Rejection of Claims 10-14 and 25-28 Under 35 U.S.C. § 112, Second Paragraph

Claims 10-14 and 25-28 were rejected under 35 U.S.C. § 112, second paragraph, for being allegedly indefinite.[27] Applicant traverses since the specification fully explains the claims' scope using language which is understood by one of ordinary skill in the art, as demonstrated by Dr. Williams' declaration, as discussed below.

The Examiner continued to find the term "at least a portion" indefinite for two reasons. First, the Examiner argued that "the artisan would not necessarily *know* which portions would

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[24] Office Action, page 3, first paragraph.

[25] Dr. Williams' declaration, paragraph 6.

[26] Dr. Williams' declaration, paragraph 7.

[27] Office Action, pag 3, second full paragraph.

result in neutralizing antibodies, so the portions would not be *understood* by the artisan."[28] This argument confuses the requirement of **definiteness** under 35 U.S.C. §112, second paragraph with that of **enablement** under 35 U.S.C. §112, first paragraph. The MPEP directs the Examiner that:

"Breadth of a claim is not to be equated with indefiniteness."[29]

The Examiner suggests that the artisan would not "know" which portions produces neutralizing antibodies. This is not the test of definiteness. Definiteness does not rest on "knowledge" of such portions but whether the meaning of the term "at least a portion" (regardless of the actual sequence or structure of the portion which falls within this meaning) is understood by one of ordinary skill in the art. As previously discussed in the November Amendment, one of skill in the art understands from the specification that the term "at least a portion of" a toxin defines fragments which range in size from 4 amino acids to the entire amino acid sequence of the toxin. This definition is sufficiently precise to satisfy the definiteness requirement.

Second, the Examiner argued that the term "at least a portion of " is indefinite because "the artisan does not definitely know what the final immunogen consists of."[30] Again, this argument testifies to the Examine's confusion over the distinction between the requirements for definiteness and for enablement. Definiteness under 35 U.S.C. §112, second paragraph, does not require **definite** knowledge as the examiner appears to suggest. Rather, what is required is **reasonable** particularity and distinctness in language. This requirement is recognized by the MPEP which directs the Examiner that:

> ". . . he or she should allow claims which define the patentable subject matter with a *reasonable* degree of particularity and distinctness."[31]

The scope of the subject matter embraced by the claim term "at least a portion of" a toxin is clear to one of ordinary skill in the art as demonstrated by Dr. William's declaration:[32] this

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28 (Emphasis added) Office Action, paragraph bridging pages 3 and 4.

29 MPEP 2173.04 citing *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971).

30 Office Action, page 4, first full paragraph.

31 (Emphasis added) MPEP 2173.02.

32 Dr. Williams' declaration, paragraphs 8 and 9.

term is understood by the artisan to mean fragments which range in size from 4 amino acids to the entire amino acid sequence of the toxin. Indeed the understanding of one of skill in the art of this meaning is not disputed by the Examiner. The statute does not require, and the Examiner cannot ask for, more than such understanding. Accordingly, the term "at least a portion of" a toxin is not indefinite, and the rejection of Claims 10-14 and 25-28 under 35 U.S.C. §112, second paragraph should be withdrawn.

3. Rejection of Claims 10-14 and 25-28 Under 35 U.S.C. § 103

Claims 10-14 and 25-28 were rejected under 35 U.S.C. § 103(a) for alleged obviousness over Thompson *et al.* in view of Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel.[33] Applicant traverses because of the Examiner's continued failure to establish a *prima facie* case of obviousness. Moreover, even assuming, for the sake of argument, that a *prima facie* case of obviousness is established, Applicant rebuts with evidence of non-obviousness.

A. A *prima facie* case of obviousness is not established

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, (b) discloses the elements of the claimed invention, and (c) provides a reasonable expectation of success should the claimed combination be carried out.[34] Failure to establish any **one** of these requirements is, without more, a failure to meet the Examiner's burden. The Examiner's arguments advanced in the final Office action continue to fail to establish **each of the three** requirements, thus entitling Applicant to withdrawal of this rejection.

Applicant notes that the following arguments focus on independent amended Claim 10 since nonobviousness of an independent claim necessarily leads to nonobviousness of any claim depending therefrom.[35]

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[33] Office Action, page 4, second full paragraph.

[34] See, *e.g.*, *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

[35] MPEP 2143.03, citing *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

i. There Is No Motivation To Combine The References' Teachings To Produce The Claimed Vaccines - *In re Rouffet*

In a recent Federal Circuit decision, the Court found that it is improper for the Patent Office to consider references collectively **before** establishing the threshold requirement that a person skilled in the art would be **motivated** to combine these references in the first place. This threshold requirement avoids improper use of the invention itself and hindsight reconstruction to defeat patentability. Specifically, the Federal Circuit explained:

> "To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires that examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."[36]

However, while the Examiner recognized the requirement for motivation by the prior art,[37] his arguments in support of why such motivation exists are defective, as discussed below.

First, the Examiner disputed Applicant's assertion that the methods of making vaccines which are taught by LeClerc *et al.* and Kleid are irrelevant to obviousness of the vaccines of Claim 10.[38] In rebutting Applicant's assertion, the Examiner contended that "the *methods* of the references have resulted in vaccines that make the compound of the claims obvious."[39] This rebuttal it is based on the Examiner's failure to observe Federal Circuit law. The Federal Circuit has held that the existence of a method for making a composition is irrelevant to obviousness of the composition. It stated that:

> "the existence of a general method of isolating [a composition] . . . is essentially irrelevant to the question whether the specific [composition] . . . would have been obvious, in the absence of other prior art that suggests the

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[36] *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. (1998).

[37] The Examiner recognized that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." Office Action, page 6, first full paragraph, citing *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

[38] Office Action, page 5, second full paragraph.

[39] (Emphasis added) *Id.*

> claimed [composition] . . . There must, however, still be prior art that suggests the claimed compound in order for a *prima facie* case of obviousness to be made out."[40]

Amended Claim 10 recites a vaccine, not a method of making a vaccine. In conformity with Federal Circuit law, the methods taught by LeClerc *et al.* and Kleid are irrelevant to obviousness of the vaccines of amended Claim 10.

The Examiner recognized the principle that the distinction between the claimed invention and the prior art must be assessed and resolved to determine whether the invention would have been obvious at the time it was made.[41] Nonetheless, the Examiner declined to apply this principle to the cited references. Thus, the Examiner merely stated that LaPenotiere *et al.* teaches "fusion proteins of *Clostridium botulinum* toxin and maltose binding protein."[42] No assessment, however, was made of the differences between LaPenotiere *et al.*'s fusion protein and the claimed fusion protein of amended Claim 10.[43] Instead, the Examiner advanced the unsupported conclusion that vaccines taught by LaPenotiere *et al.* "render the vaccine of the claims obvious."[44] In the absence of assessment of the distinctions between this (and every other) reference and amended Claim 10's invention, a conclusion of obviousness cannot properly be reached.

The Examiner bestowed similar dismissive treatment of the remaining references by declaring that "Vaccines taught in . . . [Roitt, LeClerc *et al*, and Kleid] render the vaccine of the claims obvious."[45] This sentence concludes that the invention is obvious without supporting rationale. Differently stated, the Examiner proposes that the simple fact that a reference discloses "fusion proteins comprising toxin proteins" automatically makes obvious amended Claim 10's **particular** vaccine which are both soluble and neutralizing. This

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[40] *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995).

[41] Office Actio, page 5, second full paragraph.

[42] Office Action, sentence bridging pages 5 and 6.

[43] Importantly, LaPenotiere *et al.* discloses a fusion protein in which a fragment of *Clostridium botulinum* type A toxin (**not** type B and/or type E toxins as recited in Claim 10) is fused to maltose binding protein (MBP).

[44] Office Action, page 6, first full sentence.

[45] Office Action, page 6, first full sentence.

proposal must fail since an explanation of the nexus between the teachings of the various references and the claimed vaccines is required, and in this instance, lacking.

For example, the Examiner is silent on **why** one of skill in the art would be motivated to make amended Claim 10's vaccine by combining Roitt's hypothetical fusion protein (in which an antigen is fused to the hydrophobic membrane region of IgM) with any other reference. This is particularly so since Roitt only **hypothesized** that its fusion protein may (but not necessarily) function as a vaccine.[46] However, no evidence of such function was advanced either by Roitt or the Examiner.

Likewise, not a word is offered on **why** the artisan would be motivated to make amended Claim 10's fusion proteins by combining LeClerc *et al.*'s fusion protein, in which an epitope from poliovirus or from hepatitis B virus is fused with maltose binding protein, with the teaching of any other reference.

Similarly, there is no explanation **why** the mere disclosure of Kleid's fusion protein, in which one of the structural proteins (VP_1) of the foot-and-mouth disease virus is ligated to a peptide encoded by the *E. coli* tryptophan operon, motivates combining this reference with any other reference to make amended Claim 10's fusion protein in which a non-toxin protein sequence is ligated to at least a portion of *Clostridium botulinum* type B toxin and/or type E toxins.

The Examiner next addressed Applicant's argument that there is "no motivation to substitute the formalin-inactivated toxin E of Siegel with the claimed invention's fusion protein."[47] The Examiner argued that such motivation exists because "there *is* knowledge generally available to one of ordinary skill in the art" since recombinant fusion proteins offer several advantages.

Prior to discussing these purported advantages, Applicant notes that amended Claim 10 does not relate merely to a fusion protein, but to a fusion protein which is both soluble and neutralizing. This distinction is important because the advantages of **fusion proteins** (which may or may not be soluble and neutralizing) do not explain why (if at all) the various and

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[46] Roitt, page 178, column 1.

[47] Office Action, page 6, first full paragraph; November Amendment, page 13.

sundry disclosures of Thompson *et al.*, Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel should be combined to produce the **soluble and neutralizing vaccines** of amended Claim 10.

The first advantage proposed by the Examiner was of large scale production has nothing to do with the claims as written. Moreover, the Examiner does not explain why (if at all) substituting Siegel's formalin-inactivated toxin E with Claim 10's toxin E would affect the large scale production of fusion proteins containing these toxins; whether large scale production of a fusion protein is possible cannot be predicted from the nature of the fusion partners.

The second advantage proposed was of incorporating a desirable characteristic such as a highly immunogenic epitope. Nonetheless, such advantage still does not explain why Siegel's formalin-inactivated toxin E would be substituted for amended Claim 10's toxin E. This is because introducing this desirable characteristic would involve changes to the fusion partner of the toxin, rather than to the toxin itself.

The third advantage presented by the Examiner was of purification. Again, this advantage would be achieved by substituting the fusion partner of the toxin (not the toxin *per se*), and does not explain a motivation to substitute Siegel's formalin-inactivated toxin E with amended Claim 10's toxin E.

The Examiner then introduced Nygren *et al* in support of the reference's teaching of other advantages of recombinant fusion proteins.[48] However, since Nygren *et al.* discusses the advantages of affinity purification of fusion proteins on an industrial scale, which are essentially the same as the first and third advantages discussed above, this reference does not provide the necessary motivation to substitute Siegel's formalin-inactivated toxin E with amended Claim 10's toxin E for the same reasons advanced *supra*.

Based on the above, it is submitted that the Examiner has not met her burden of explaining why there is a suggestion in each of the cited references to combine its teachings with those of the other references to arrive at the vaccines of amended Claim 10. Importantly, the Examiner does not explain how references which do **not disclose** the complete sequences of both *Clostridium botulinum* type B and type E toxins can logically be combined to arrive at the claimed vaccines which require these sequences as an **essential element**.

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[48] Office Action, page 6, first full paragraph.

In addition to continuing to fail to satisfy the "motivation to combine the references" prong of a *prima facie* case of obviousness, the Examiner has also failed in her duty to address all Applicant's arguments presented in the November Amendment in support of a lack of such motivation. The MPEP directs the Examiner that:

> "The examiner *must* address all arguments which have not already been responded to in the statement of the rejection."[49]

For example, the Examiner has not responded to the following arguments: (a) the teachings of Binz *et al.* are irrelevant since its teaches the sequence of type A toxin (which is not recited in amended Claim 10) and of only a partial (rather than the complete) sequence of Type E toxin;[50] (b) unclear relevance [if any] of Roitt's teaching that "recombinant antigens can be generated such as viral epitopes and synthetic peptides,"[51] (c) lack of relevance of substituting the fusion protein type A toxin with the pentavalent botulinum (ABCDE) toxoid vaccine of Siegel when type A toxin is not recited in amended Claim 10;[52] (d) the skilled artisan would not include in Siegel's vaccine a fusion protein comprising type B toxin to arrive at amended Claim 10's vaccine, particularly in view of Siegel's disclosure that the "human response to two lots of the MDPH product was *significantly greater* than to the PDC product for the type B component;"[53] and (e) Kleid's statements teach away from substituting Siegel's formalin-inactivated type B and type E toxins with the fusion proteins recited in amended Claim 10.[54] The Examiner's failure to rebut Applicant's arguments is an admission of the arguments' persuasiveness. It is submitted that Applicant's unrebutted arguments are sufficient to negate a *prima facie* case of obviousness.

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[49] (Emphasis added) MPEP 707.07.

[50] November Amendment, page 12, first paragraph.

[51] November Amendment, page 12, second paragraph.

[52] November Amendment, page 13, first full paragraph.

[53] November Amendment, page 13, third full paragraph.

[54] November Amendment, paragraph bridging pages 13 and 14.

ii. The Combined References Do Not Teach All The Elements of The Claimed Invention

A *prima facie* case of obviousness cannot be established absent a teaching or suggestion of "all the claim limitations" by the prior art."[55] As discussed in the November Amendment, none of Thompson *et al.*, Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel teaches amended Claim 10's limitation of a fusion protein comprising **both** a non-toxin protein sequence, as well as *Clostridium botulinum* type B toxin and/or type E toxin.

The Examiner argued that "[i]n response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references."[56] This statement mischaracterizes Applicant's arguments. It is controlling Supreme Court law that :

> "Under § 103, the scope and content of the prior art are to be determined . . . [and] differences between the prior art and the claims at issue are to be ascertained . . ."[57]

Applicant did not argue the content of the prior art individually. Rather, in conformance with Supreme Court law, Applicant analyzed the scope and content of each cited reference, then compared this scope and content to the **collective** (not individual) teachings of the references to the claims prior to concluding that the **collective** teachings of the references are silent on two essential elements of amended Claim 10, *i.e.*, the complete amino acid sequence of *Clostridium botulinum* type B toxin and type E toxin.

Indeed, the Examiner's analysis of the threshold "all elements" requirement of a *prima facie* case of obviousness falls short of even that which she erroneously accuses Applicant of doing; the Examiner did not even consider the "scope," "content," and "differences" (as she must under Supreme Court law) as evidenced by her failure to note that these references do **not** disclose the complete amino acid sequence of each of *Clostridium botulinum* type B toxin and type E toxin.

In responding to Applicant's comments in the November Amendment regarding failure of the references to teach all the elements of the claimed invention, the Examiner also

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[55] MPEP 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

[56] (citations omitted) Office Action, paragraph bridging pages 4 and 5.

[57] *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966).

disagreed with Applicant's assertion that "references to type A toxin are irrelevant" to obviousness of independent amended claim 10 since amended claim 10 refers only to toxin types B and E, but not type A.[58] This mischaracterizes Applicant's argument because Applicant did not assert the lack of relevance of any of the references in so far as they purportedly teach all the elements of amended Claim 10; rather, Applicant considered (both in the November Amendment and in this communication) the teaching of **each** of the references (whether or not they disclose type A toxin) prior to concluding that none teaches the limitations (*i.e.*, type B toxin and/or type E toxin sequences) which are **recited** in amended Claim 10. Applicant's assertion of the lack of relevance of references which teach type A toxin was advanced only in discussing two of the three prongs of a *prima facie* case of obviousness, namely the motivation to combine the references' teachings[59] and the reasonable expectation of success.[60]

The Examiner explained that her disagreement rests on the observation that "Claim 10 recites, 'a vaccine *comprising* ...' and thus would encompass type A toxin, for example."[61] This explanation conveys the Examiner's lack of appreciation of the "all elements" prong of the three-prong test of the sufficiency of a *prima facie* case of obviousness. Rather than looking to what elements **may** be included in the claim, the first prong requires that all the elements which are **actually recited** in the claims be taught or suggested in the collective disclosures of the cited references. What **is** recited in amended Claim 10 is the limitation that a fusion protein comprise **both** a non-toxin protein sequence, as well as at least a portion of *Clostridium botulinum* type B and/or type E toxins. The Examiner does not allude to where (if at all) any of the cited references teaches or suggests **these recited** limitations. This is her burden, and she has not satisfied it. Furthermore, the Examiner's observation that Claim 10 encompasses type A toxin because this claim uses the term "comprising" does not cure the simple fact that the references do not teach, which they must, the elements which **are** recited in amended Claim 10.

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[58] Office Action, page 5, first full paragraph.

[59] November Amendment, item 5.B. on pages 10-15.

[60] November Amendment, item 5.c. on pages 15-16.

[61] (Emphasis in original) *Id.*

Because of the Examiner's failure to establish the "all elements" requirement of a *prima facie* case of obviousness, rejection of Claims 10-14 and 25-28 cannot stand. Its withdrawal is respectfully requested.

iii. The Combined References Do Not Teach A Reasonable Expectation Of Success In Practicing The Claimed Vaccines

The Examiner also failed to establish that the references teach a reasonable expectation of success in producing the claimed vaccines. The Examiner's singular response to Applicant's arguments was that "However, certainly the fusion proteins discussed as therapeutic agents in Roitt, LeClerc *et al*, Kleid, LaPenotiere *et al.* and Nygren *et al.* are all examples of *successful vaccines.*"[62]

This statement is incorrect. Roitt does **not** disclose a successful vaccine. Roitt discusses different strategies for producing vaccines (*e.g.*, killed organisms, live attenuated organisms, and individual antigens). The only colorable reference Roitt makes to fusion proteins as vaccines is speculative; Roitt says:

> "A rather cunning way to improve the performance of a relatively weak immunogen is to stitch the gene segment encoding the hydrophobic membrane region of IgM onto the C-terminus of the antigen gene so giving the molecule an anchor to hold it in the membranes, particularly of dendritic cell and macrophages, where *presumably* it will be very effectively presented to antigen-specific lymphocytes."[63]

Thus, at best, Roitt hypothesized a method of improving the antigenicity of an immunogen by fusing it to an IgM segment. Roitt neither made nor tested the success of this hypothetical fusion protein as a soluble and neutralizing vaccine. Accordingly, Roitt does not teach "successful vaccines."

Importantly, also, the Examiner's statement is tantamount to asserting that since the prior art documents disclosed vaccines containing fusion proteins, one skilled in the art might find it obvious to try the particular combination of amended Claim 10 of a vaccine containing at least a portion of *Clostridium botulinum* type E and/or type B toxins fused to a non-toxin

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[62] (Emphasis added) Office Action, page 6, final paragraph.

[63] (Emphasis added) Roitt, page 178, column 1.

protein. However, this is not the standard of 35 USC 103. Indeed, the "obvious to try" argument has been thoroughly discredited by the Federal Circuit:

> "[T]his court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under Section 103."[64]

Because the Examiner's conclusion of a reasonable expectation of success in producing the claimed vaccines rests on an improper legal standard, this conclusion is erroneous.

Furthermore, the Examiner does not point to where the prior art teaches a reasonable expectation of success in generating the claimed vaccines which contain the claimed combination of non-toxin protein fused with *Clostridium botulinum* type E and/or type B toxins. The law is that:

> " . . . the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."[65]

Specifically, the Examiner does not point to where the prior art suggests a reasonable expectation of success in substituting any one of LeClerc *et al.*'s poliovirus epitope or hepatitis B virus epitope, Kleid's foot-and-mouth disease virus VP_1 protein, and Penotier's fragment of *Clostridium botulinum* type A toxin with amended Claim 10's at least a portion of *Clostridium botulinum* type B and/or type E toxin to produce a soluble and neutralizing vaccine.

Because the Examiner applied an improper legal standard and misapplied a correct standard, a reasonable expectation of success in producing the vaccines of amended Claim 10 is lacking. Indeed, there can be no reasonable expectation of success as explained by Dr. William's declaration which is further discussed below. The deficiency of the Examiner's showing alone negates a *prima facie* case of obviousness.

In addition to failing to establish the third prong of a *prima facie* case of obviousness, the Examiner also failed to rebut all Applicant's arguments presented in the November Amendment that a "reasonable expectation of success" is lacking. For instance, the Examiner did not allude to Applicant's following arguments: (a) availability of methods for making vaccines is irrelevant to obviousness of vaccine compositions, (b) Kleid teaches away from using fusion proteins as vaccines, and (c) the Examiner relied on impermissible hindsight

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[64] *See In re O'Farrell*, 7 USPQ2d 1673, at 1680-1681 (Fed. Cir. 1988).

[65] *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) as cited in *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

guidance from the application. The Examiner's failure to rebut these arguments is an admission that they are compelling. It is submitted that Applicant's unrebutted arguments in the November Amendment negate the "reasonable expectation of success" prong of a *prima facie* case of obviousness.

Based on the above, a *prima facie* case of obviousness is not established because none of its elements are satisfied. Withdrawal of the rejection of Claims 10-14 and 25-28 under 35 U.S.C. § 103 is thus respectfully requested.

B. Evidence in Rebuttal of a *prima facie* case of obviousness

While Applicant need not present rebuttal evidence when a *prima facie* case of obviousness is not made, nonetheless, in the interest of expediting Applicant's business interests, Applicant presents the declaration of Dr. Williams in support of unexpected properties of the claimed invention.

Dr. Williams is an expert, and is qualified to speak on the level of ordinary skill, in the fields of molecular biology, biochemistry and immunology. In his declaration, Dr. Williams states that the vaccines recited in independent amended Claim 10 have two unexpected properties, namely **solubility** and **neutralizing** activity, in view of the cited prior art.

With respect to the unexpected solubility of the claimed vaccines, Dr. Williams' declaration explains that such solubility was unexpected since (a) the prior art, as exemplified by La Penotier *et al.*, taught that a fusion protein of *Clostridium botulinum* type A toxin C fragment and maltose binding protein (MBP) was **insoluble**, thus suggesting that other fusion proteins containing at least a portion of *Clostridium botulinum* type B and/or type E toxins would also be insoluble,[66] (b) Dr. Williams' preliminary experimental work which demonstrated the **insolubility** of two *Clostridium botulinum* fusion proteins, one of which falls within the scope of independent amended Claim 10,[67] and (c) the **solubility** of the claimed

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[66] Dr. Williams' declaration, paragraph 11.

[67] Williams' declaration, paragraph 12.

vaccines was arrived at empirically rather than on the basis of the cited prior art's disclosure.[68]

As to the unexpected neutralizing activity of the claimed vaccines, Dr. Williams' declaration establishes that this activity was surprising because (a) the prior art, as exemplified by Kleid, taught that generation of neutralizing antibodies was not *ipso facto* expected as a result of the mere generation of a fusion protein,[69] (b) the prior art, as exemplified by Acheson *et al.*, taught that antibodies against a toxin protein are not necessarily neutralizing,[70] (c) Dr. Williams' experimental work which failed to generate neutralizing antibodies with either soluble or insoluble toxins derived from *Staphylococcus aureus* and from *Clostridium difficile*,[71] and (d) the neutralizing activity of the claimed vaccines was arrived at empirically and not on the basis of the cited prior art.[72]

Because a factually supported declaration by one skilled in the art must be considered by the Examiner,[73] Dr. William's declaration rebuts a *prima facie* case of obviousness (if such a case were arguably made by the Examiner). Accordingly, it is respectfully requested that the rejection of 10-14 and 25-28 under 35 U.S.C. § 103 be withdrawn.

4. Rejection of Claims 13 And 14 Under 35 U.S.C. § 103

Claims 13 and 14 were further rejected for obviousness under 35 U.S.C. § 103 based on Thompson *et al.*, in view of Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel and further in view of Ford *et al.* Applicant cannot agree because a *prima facie* case of obviousness is not established. Furthermore, even assuming, *arguendo*, that a *prima facie* case of obviousness is established, Applicant rebuts with evidence of non-obviousness.

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[68] Dr. Williams' declaration, paragraphs 12 and 17.

[69] Williams' declaration, paragraph 13.

[70] Williams' declaration, paragraph 14.

[71] Dr. Williams' declaration, paragraph 15.

[72] Williams' declaration, paragraphs 16 and 17.

[73] *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

A. A *prima facie* case of obviousness is not established

The Examiner has failed to establish each of the three requirements of a *prima facie* case of obviousness as discussed below.

i. The Combined References Do Not Disclose All The Elements Of Claims 13 and 14

As discussed above, the threshold requirement in a *prima facie* case of obviousness is the provision of references which disclose all the limitations of the claimed invention.

In the November Amendment, Applicant argued that, as to both amended Claims 13 and 14, **none** of Thompson *et al.*, Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, Siegel and Ford *et al.* alone or in combination, discloses the complete amino acid sequence of *Clostridium botulinum* type B toxin and type E toxin. Applicant also argued that, with regard to amended Claim 14, the cited combination of references suffers from the additional shortfall of failing to disclose the element of "substantially endotoxin-free" vaccines.

The Examiner did **not rebut** Applicant's arguments either by pointing to specific teachings of the references, or by providing additional references which provide the missing disclosure. In the absence of such rebuttal, Applicant's arguments are conceded. A *prima facie* case of obviousness thus must fall.

ii. There Is No Motivation To Combine The References To Make The Claimed Vaccines Which Contain Fusion Proteins Comprising a Poly-Histidine Tract, Or Which Are Substantially Endotoxin-Free

As discussed above, the Examiner bears the burden of providing an explanation based on logic and sound scientific reasoning, as well as providing sufficient impetus to lead one of ordinary skill in the art to combine the teachings of the references to make the claimed vaccines.[74] This burden has not been met with respect to either amended Claim 13 or 14.

As discussed above with respect of the rejection of Claims 10-14 and 25-28, the Examiner does not explain how the claimed vaccines which require as an **essential element**,

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[74] *Ex parte Levengood*, 28 USPQ2d 1300, 1301 (Pat. Bd. Appeals & Interf. 1993).

knowledge of the complete sequences of both *Clostridium botulinum* type B and type E toxins can be made obvious by combining references which **do not disclose** this essential element.

Additionally, the Examiner has failed to rebut Applicant's following arguments which were advanced in the November Amendment in support of lack of "motivation" to combine the references' teachings: (a) Binz *et al.* is irrelevant since its teaches the sequence of type A toxin (which is not recited in Claim 13) and of only a partial (not the complete) sequence of Type E toxin; (b) unclear relevance [if any] of Roitt's teaching that "recombinant antigens can be generated such as viral epitopes and synthetic peptides," (c) lack of relevance of substituting the fusion protein type A toxin with the pentavalent botulinum (ABCDE) toxoid vaccine of Siegel when type A toxin is not recited in amended Claim 10; (d) the skilled artisan would not include in Siegel's vaccine a fusion protein comprising type B toxin to arrive at Claim 13's vaccine, particularly in view of Siegel's disclosure that the "human response to two lots of the MDPH product was *significantly greater* than to the PDC product for the type B component;" (e) Kleid's statements teach away from substituting Siegel's formalin-inactivated type B and type E toxins with the fusion proteins recited in amended Claim 13,[75] (f) no advantages were advanced in support of substituting the maltose binding protein (MBP) of LeClerc's fusion protein with the poly-histidine of amended Claim 13's fusion protein,[76] (g) there is no explanation why the biological activity of amended Claim 13's fusion proteins as neutralizing vaccines may be predicted from the neutralizing activity of prior art fusion proteins in which each of the fusion partners is different,[77] and (h) under *In re Deuel*,[78] a general incentive to keep the vaccine endotoxin-free does not make obvious the

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[75] These arguments were incorporated by reference in the November Amendment, page 18, first and second paragraph.

[76] November Amendment, page 19, first full paragraph. While the Examiner stated in the Office Action mailed May 28, 1997 that "one would have been motivated to substitute poly histidine for the maltose binding proteins of LeClerc *et al* in order to facilitate purification of the fusion protein and thus ensure large quantities of pure immunogen," this is not an "advantage" which provides a motive since LeClerc's poly-histidine fusion partner already provides these benefits, and thus the artisan would not be motivated to substitute it with another fusion partner; rather, the artisan would be motivated to retain poly-histidine as a fusion partner because it is already shown to provide these benefits.

[77] November Amendment, page 19, second full paragraph.

[78] *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995).

particular endotoxin-free vaccines of amended Claim 14.[79] The Examiner's failure to rebut the above-listed arguments is a concession that they are convincing. Applicant's unrebutted arguments are sufficient to negate both a motivation to combine the cited references, and a *prima facie* case of obviousness.

iii. There Is No Expectation Of Success In Making the Claimed Vaccines Which Contain Fusion Proteins Comprising a Poly-Histidine Tract, Or Which Are Substantially Endotoxin-Free

The burden is squarely placed on the Examiner to establish an expectation of success in practicing the claimed invention. This has not been done.

The Examiner asserted that there is a reasonable expectation of success in making vaccines which contain fusion proteins comprising a poly-histidine tract or making endotoxin-free vaccines, because "the references themselves teach the success of such endeavors."[80] However, this statement reads more into the cited prior art than is there. The cited prior art which discusses vaccines[81] discloses only a reasonable expectation of success of the endeavors which are specific to the vaccines of the prior art, but not to the claimed vaccines. Specifically, LeClerc *et al*, Kleid *et al*, and Siegel *et al.* suggest that there is a reasonable expectation of success in generating vaccines to poliovirus type 1, hepatitis B virus, VP1 of FMD virus, and type A, B, C, D and E toxins of *Clostridium*. However, none of these references suggests a reasonable expectation of success in generating the claimed neutralizing vaccines which comprise at least a portion of type B and/or E toxins of *Clostridium botulinum*. Indeed, any alleged expectation of success is contradicted by Dr. Williams' attached declaration which is further discussed below.

From the above, a *prima facie* case of obviousness is not established because none of its elements are satisfied. Withdrawal of the rejection of Claims 13 and 14 under 35 U.S.C. § 103 is thus respectfully requested.

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[79] November Amendment, page 19, third and fourth paragraphs.

[80] Office Action, page 8, first full paragraph.

[81] Only LeClerc *et al.*, Kleid, and Siegel discuss generation of vaccines, while Thompson *et al.*, Binz *et al.*, Roitt, and Ford *et al.* do not.

B. Evidence in Rebuttal of a *prima facie* case of obviousness

While evidence in rebuttal of a *prima facie* case of obviousness is not required since such a case was not made, Dr. Williams' declaration is nonetheless presented, in the interest of expediting Applicant's' business interests, to rebut any alleged *prima facie* case of obviousness.

Specifically, the Examiner disagreed with Applicant's position that "Ford *et al.* teaches use of fusion proteins for the recovery and purification of proteins, not for the generation of antibodies."[82] This was based on the Examiner's assertion that "in a 103 rejection, it is permissible to cite a reference that uses the product for a different reason than the *claimed invention*."[83] The Examiner is respectfully reminded that even if the prior art uses the claimed invention for a different purpose from that claimed, rebuttal of a *prima facie* case is nonetheless successful if there a showing that:

> "[the claimed compositions] had properties not possessed by the prior art compositions or that they possessed them to an unexpectedly greater degree."[84]

As discussed above,[85] Dr. Williams' declaration establishes that the claimed vaccines possessed not one, but at least two unexpected properties compared to prior art compositions, i.e, solubility and neutralizing activity. In view of this evidentiary showing, a *prima facie* case of obviousness is rebutted and the vaccines of Claims 13 and 14 are nonobvious. Withdrawal of the rejection of these claims under 35 USC § 103 is thus respectfully requested.

Conclusion

All grounds of rejection and objection of the Office Action of October 15, 1998 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview

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[82] Office Action,page 7, third paragraph.

[83] (Emphasis added) *Id.*

[84] *In re Linter*, 173 USPQ 560, 173 (CCPA 1972); *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

[85] Item 3.B. on page **21** of this communication.

would aid in the prosecution of this application, the Examiner is encouraged to call Peter G. Carroll collect at (617) 252-3353.

Dated: April 15, 1999

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APPENDIX I
PENDING CLAIMS AS AMENDED IN THIS COMMUNICATION

10. (Twice Amended) A soluble and neutralizing vaccine comprising a fusion protein, said fusion protein comprising a non-toxin protein sequence and at least a portion of one or more *Clostridium botulinum* toxins, said one or more toxins selected from the group consisting of type B toxin and type E toxin.

11. (Once Amended) The soluble and neutralizing vaccine of Claim 10 further comprising a fusion protein comprising a non-toxin protein sequence and at least a portion of *Clostridium botulinum* type A toxin.

12. (Once amended) The soluble and neutralizing vaccine of Claim 10, wherein said portion of said *Clostridium botulinum* toxin comprises the receptor binding domain.

13. (Once amended) The soluble and neutralizing vaccine of Claim 10 wherein said non-toxin protein sequence comprises a poly-histidine tract.

14. (Once amended) The soluble and neutralizing vaccine of Claim 10, wherein said vaccine is substantially endotoxin-free.

25. (Once Amended) The soluble and neutralizing vaccine of Claim 10, wherein said vaccine is protective against a challenge with said one or more *Clostridium botulinum* toxins.

26. (Once amended) The soluble and neutralizing vaccine of Claim 11, wherein said vaccine is protective against a challenge with said *Clostridium botulinum* type A toxin.

27. (Once amended) The soluble and neutralizing vaccine of Claim 10, wherein said portion of *Clostridium botulinum* type B toxin is selected from the group consisting of SEQ ID NO:44 and SEQ ID NO:46, and said portion of *Clostridium botulinum* type E toxin is selected from the group consisting of SEQ ID NO:54 and SEQ ID NO:56.

28. (Once amended) The soluble and neutralizing vaccine of Claim 11, wherein said portion of *Clostridium botulinum* type A toxin is selected from the group consisting of SEQ ID NO:26 and SEQ ID NO:36.